DETAILED ACTION

An amendment was filed on 3/11/09.

Claims 54-64 and 69-72 were canceled and claims 73-85 were added.

Claims 65-68 and 73-85 are pending.

Claims 66 and 67 stand withdrawn as being drawn to an non-elected invention. New claims 76 and 77 are similarly withdrawn.

Claims 65, 68, 73-75 and 79-85 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 65, 68, 73-75 and 79-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 65 and 68 are drawn to methods of controlling the metastatic or migrational activity of tumor or cancer cells by contacting tumor or cancer cells with a composition comprising an siRNA that inhibits the activity of PRF1. PRF1 was also known in the prior art as REDD1, RPT801, and HOG18.

Claims 73-75 and 79-85 are drawn to methods of inhibiting the growth of tumor cells of a precancerous growth having dysregulation of PI-3-kinase signaling and hyperactivation of the HIF-1alpha signaling pathway, and/or hyperactivation of AKT signaling, by administering to a subject a composition comprising an siRNA that inhibits the activity of PRF1.

None of the claims limits the mode of administration.

The instant invention is based on the observations that transcription of PRF1 is regulated by one or more of the diverse PI3K signaling pathways, and that inhibition of PRF1 expression in PC-3 prostate cancer cells resulted in a decrease in cell growth. The specification presents evidence that this transcriptional activation occurs downstream of HIF1 alpha and Akt in two of the myriad PI3K pathways, and that PRF1 is located downstream of mammalian target of rapamycin (mTOR) in the PI3K network, but provides no further guidance as to the biochemical function of PRF1.

PI3Ks constitute a family of enzymes that respond to stimuli from various receptors to produce 3' phosphoinositide lipids that act as second messengers by binding to diverse cellular target proteins to influence a variety of cellular activities including proliferation, differentiation, chemotaxis, survival/apoptosis, intracellular trafficking, and glucose homeostasis. See Katso et al (Annu. Rev. Dev. Biol. 17: 615-675, 2001). Katso states that the factors that determine which cellular function is mediated by a PI3K are complex and may be partly attributed to the diversity that exists at each level of the PI3K signaling cascade, such as the type of stimulus, duration of stimulus, the isoform of PI3K, the nature and intracellular location of the second

messenger lipids, and the developmental state of the cell or organism. Further, the spatial and temporal aspects of PI3K signaling, functional redundancy, and crosstalk with other signaling networks are also thought to influence the integration of a given stimulus. See abstract, and page 655, first paragraph of Perspective.

Fig. 1 at page 624 of Katso gives some idea of the enormous complexity of PI3K signaling. Stimuli, both positive and negative, include Fak, shear stress, Cbl, Ruk, tyrosine kinase receptors, cytokines, integrins, cadherin, and G protein coupled receptors. Second messenger PIP_3 interacts with diverse entities including BTK/Tec kinases, PDKI, PKD, and GEFs. These interactions give rise to overlapping as well as independent cascades of activity that result in a variety of outcomes including proliferation, differentiation, chemotaxis, survival/apoptosis, trafficking, and glucose homeostasis. Note that many factors known to be involved in PI3K signaling are not even represented in the Fig (such as Akt and HIF1-alpha). Thus, those of skill in the art at the time of the invention recognized that the effects of PI3K signaling in a given cell were influenced by a complex multitude of factors that constitute nodes in a network of signaling cascades extending from PI3K that controls the activity of a variety of proteins and the transcription of various sets of genes. Possible outcomes of PI3K stimulation include opposing effects such as cellular proliferation to apoptosis.

The specification as filed teaches that PRF1 seems to be regulated by both the HIF alpha and AKT branches of the PI3K network and acts downstream of mammalian target of rapamycin (mTOR). The specification indicates that a decrease in the expression or activity of PRF1 is suitable to put a cellular system into a condition

corresponding to hypoxic conditions, which may lead to apoptosis, so inhibition of PRF1 can stimulate apoptosis for therapeutic purposes in tumor treatment. See pages 12 and 18 (paragraphs 56 and 70 of the published application). However, Fig. 1 of Katso discloses at least two other pathways by which PI3K can inhibit apoptosis (i.e. through stimulation of IKK or inhibition of BAD), and the relationship of these pathways to PRF1 is not known.

It is clear that not all aspects of the PI3K network are functional in all cells, and it follows that an agent that acts on a branch of the network that does not function in a given cell would not be expected to have any predictable effect on that cell. It is noted that the pathway steps that lead directly to regulation of PRF1 transcription or activity were not completely understood at the time of filing, and neither were the pathway steps directly downstream of PRF1 expression and activity, and its possible interactions with other signaling pathways. Accordingly, the effects of manipulating PRF1 expression were unpredictable at the time of filing, and had to be determined on a case by case basis for different tumors.

Absent information regarding which pathways are operating in a given cell at a given time, and the effects of PRF1 on those pathways, it would be completely unpredictable as to whether inhibition of PRF1 would stimulate apoptosis or not, because the effects of PRF1 inhibition on the other relevant apoptosis-affecting pathways are unknown. The specification provides no guidance in this regard, except to indicate that because PRF1 is at a downstream point in the network, it should be close to the point of action and unintended consequences should be limited. However,

the relationship of PRF1 to other branches of the PI3K network involved in apoptosis control was unknown at the time of filing, so the effects of PRF1 inhibition on cell survival were not predictable. Note also that status of PI3K independent signaling pathways that affect apoptosis and cell survival would need to be taken into account in order to accurately predict the effects of such inhibiting PRF1 (see Katso at page 656, last paragraph).

At the time the invention was filed, the in vivo function of PRF1 was not well characterized. Shoshani et al (Mol. Cell. Biol. 22(7): 2283-2293, 2002, of record) identified RTP801 (PRF1) as a novel gene encoding a protein without any defined structural domains that was upregulated sharply in glioma cells in response to hypoxia. They showed that PRF1 could either promote, or protect cells from, apoptosis and that these functions of PRF1 were dependent on the context of the cell in which it was expressed. PRF1 protected two secondary tumor cell lines from apoptosis under conditions of rapid cell division, while promoting apoptosis in both of those lines, as well as in primary non-cancerous lung parenchymal cells in vivo, under non-rapidly dividing conditions. However, Shoshani did not make a generalized conclusion that PRF1 caused apoptosis in rapidly dividing cells, but instead concluded that the involvement of PRF in pathogenic disease was complex and noted the importance of further study regarding its roles in dividing and non-dividing cells. See abstract and page 2292, last three paragraphs. Thus, prior to the time of the instant invention, it was recognized that PRF1 could either promote or inhibit cellular proliferation, depending on the context in which it was expressed. The actual biochemical function of PRF1 in PI3K signaling, i.e.

enzyme, binding factor, etc., and its relationship to other PI3K pathways affecting apoptosis was not known at the time of the invention. Absent more information as to the actual biochemical function of PFR1, and the further study indicated as important by Shoshani, it is considered unpredictable as to what would be the effects of PRF1 expression inhibition in cells generally in view of the complexity of the PI3K signaling network.

The post filing art provides further evidence of unpredictability regarding the role of PRF1 in proliferative disease. DeYoung et al (Genes Dev. 22: 239-251, 2008) showed that PRF1 (identified as REDD1) can contribute to tumor suppression in secondary tumor cells. "In vitro, loss of REDD1 signaling promotes proliferation and anchorage-independent growth under hypoxia through mTORC1 dysregulation. In vivo, REDD1 loss elicits tumorigenesis in a mouse model, and down-regulation of REDD1 is observed in a subset of human cancers." See abstract and section entitled "*Endogenous REDD1 functions to suppress tumorigenesis in vivo*" at page 246. Note that DeYoung states that a similar frequency of REDD1 downregulation was observed in a comparison of normal prostate tissue to invasive primary prostate carcinomas (citing Lapointe (Proc. Nat. Acad. Sci. 101(3): 811-816, 2004)). DeYoung concludes that "[t]aken together, these findings support the view that the endogenous REDD1 pathway... functions as a tumor suppressor mechanism in vivo" (page 246, right column, end of first full paragraph). See also Fig. 8 on page 248, which presents a model for the activity of REDD1 as a tumor suppressor. Clearly, if PRF1 (REDD1) acts as a tumor suppressor in some cells, then one of skill could not have predictably used inhibitors of

its activity to inhibit the growth of tumors or precancerous cells without further knowledge of the function of PRF1 in those particular cells.

Other prior art references provide a correlation between PRF1 expression and cancer cells as follows.

Riggins et al (US 20030207840, effective filing date 7/26/01 (US 60/307600)) identified several genes that were induced in a variety of tumor cells in response to hypoxia. These genes included HOG18 (SEQ ID NO: 5) which encodes a polypeptide identical to PRF1. Riggins suggests that conditions related to angiogenesis, such as tumor growth, could be treated by disrupting expression of HOG18. See abstract, paragraphs 9, 13, 22, 32, 33, 37, and 47; SEQ ID NOS: 5 and 6; and claims 12-14. Riggins does not provide a working example of tumor growth inhibition.

Monahan et al (US 20050037010, effective filing date 8/20/02 (US 60/404770)) taught that PRF1 (termed M22A or RTP801 by Monahan) was overexpressed in cervical cancer cells compared to normal cervical cells, and suggested that tumors could be treated with antisense that inhibits PRF1 expression. See paragraphs 62, 113, 159, 365, 368, and 371; SEQ ID NOS: 39 and 40; Table 1 at page 37; Table 5 at last line of page 38; Table 8 on page 40; and claim 40. Monahan does not provide a working example of tumor growth inhibition.

Faris et al (US 6673545) disclosed that a nucleic acid encoding instant PRF1 was overexpressed in metastatic prostate adenocarcinoma cells, relative to non-metastatic prostate adenocarcinoma cells. See Table 1 and column 4, lines 12-23. The

nucleic acid is disclosed as SEQ ID NO: 45, also denoted in Table 4 as clone ID 3120209.

In view of the facts that, at the time of the invention, the control of the cell cycle by PI3K-mediated events was considered to be extremely complicated, the role of PRF1 in this process was incompletely understood, the biochemical function of PRF1 was unknown, and PRF1 was observed to elicit opposite effects on cell survival in different contexts, it is considered to be highly unpredictable as to what the effects of PRF1 expression inhibition would have been in vivo in tumor or precancerous cells generally. This unpredictability is borne out in the post filing art (DeYoung, Lapointe, above) which suggests that PRF1 is a tumor suppressor in breast tumor cells, and is underexpressed in primary prostate carcinoma cells. Accordingly, one of skill in the art at the time of the invention could not have known generally in which primary tumor or precancerous cells in vivo the invention would function as claimed. Because the specification and prior art do not provide information as to how to predict which tumor or precancerous cells will be inhibited by PRF1 siRNA, one of skill in the art would have had to perform undue experimentation in order to practice the invention as claimed.

In addition to the unpredictability associated with the function of PRF1 in vivo, the complexity of the PI3K network, and status of the network in a given cell, those of skill in the art at the time of the invention, and after the invention, recognized significant obstacles related to the predictability of inhibiting expression of a target gene *in vivo* by RNA interference (RNAi), particularly in regards to the *in vivo* targeting and delivery of specific nucleic acids that mediate RNAi to the appropriate cell/organ, at a bio-effective

concentration and for a period of time such that said molecule is effective in inhibiting expression of a target gene. Indeed, nucleic acid based therapies at the time of filing were highly unpredictable and while it is recognized that introduction of dsRNA targeted to a specific gene may result in expression inhibition, the successful delivery of dsRNA to a target cell *in vivo*, such that the requisite biological effect was provided to the target cells/tissues/organs, must be determined empirically.

The state of the art at the time of filing shows that RNA interference was recognized as not enabled for therapeutic purposes. (See for example, Caplen 2003, Expert Opin. Biol. Ther. 2003, Vol. 3, pp. 575-586; Coburn et al. 2003, Journal of Antimicrobial Chemotherapy. Vol. 51, pp. 753-756; Agami et al. 2002 Current Opinion in Chemical Biology. Vol. 6, pp. 829-834) for reviews on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes).

Opalinska et al. (Nature Reviews Drug Discovery, 2002, Vol. 1, pp. 503-514) stated, "[i]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA", and in column 2 of the same page, "[a]nother problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general

rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Caplen (2003) taught out that, "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system…". (pg. 581).

Coburn et al. (2003) taught that the major impediment to using RNA interference as a therapeutic is that suppression of gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph).

Check (Nature, 2003, Vol., 425, pp. 10-12) reported "…scientists must figure out how to make RNAi therapies work. They are facing some formidable technical barriers, chief among which is the problem of getting siRNAs into the right cells. This is not a trivial issue, because RNA is rapidly broken down in the bloodstream and our cells don't readily absorb it through their membranes. And even when RNA gets into its target cell, scavenger proteins quickly chew it up." (see page 11, middle column, second full paragraph). Check describes that delivery methods are of concern to many researchers. In column 2 of page 11: " …'The major hurdle right now is delivery, delivery, delivery' says Sharp" and in column 3 of the same page, "Khvorova believes

that the medical benefits of RNAi will be huge if the delivery issues can be resolved. 'But we've looked at a lot of the delivery methods that have been used for antisense, and so far I haven't been impressed,' she says."

After the time of the invention, Zhang et al (Current Pharmaceutical Biotechnology 2004, Vol. 5, pp.1-7) reviewed the state of the art with regard to RNAi, and stated "[u]se of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

Thus it is abundantly clear that it was not routine prior to and after the time of the invention for those of skill in the art to perform therapy by delivery of siRNA to target cells in vivo, particularly by methods other than those that allow delivery directly to the target cells.

In particular regards to Applicant's *ex vivo* example, often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al (Agrawal et al. (Mol. Med. Today 6:72-81, 2000) stated "[t]he cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*in vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of

an antisense oligonucleotide." Agrawal discussed these factors in relation to antisense, but they would also apply to dsRNA. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies").

In regards to the amount of direction provided by Applicant as to how one of skill in the art would practice the full scope of the claimed invention, the specification as filed does not disclose any delivery formulations or techniques that were not available in the prior art, and so does not adequately address the state of the art at the time of the invention with regard to siRNA delivery to target cells in vivo.

Given the recognized unpredictability in the art of nucleic acid therapeutics, one of skill would still require specific guidance to practice the claimed methods *in vivo* in any organism or any mammal, with the resultant specified biological effect. However, the specification does not provide either examples or the required guidance to allow one of skill in the art to reliably and predictably obtain success using the claimed methods *in vivo*. The specification does not overcome the art recognized obstacles to *in vivo* RNAi, particularly in terms of specific targeting and delivery of the dsRNA to a whole organism. As a result one of skill in the art would have to perform undue experimentation in order to practice the claimed invention.

Based on the instant disclosure, one of skill in the art would not know, *a priori*, if practicing of the instant method comprising introducing a siRNA of the invention, *in vivo*, to a whole organism, would result in the successful inhibition of the target gene in any

particular cell, tissue or organ of said organism. After considering the totality of evidence, in particular the unpredictability associated with the function of PRF1 in vivo, the complexity of the PI3K network, the status of the network in a given cell, and the systemic delivery of siRNAs in vivo, as well as the states of these arts, and the amounts of exemplification and guidance in the specification, the Office finds that one of skill in the art could not practice the invention was claimed without undue experimentation.

Response to Arguments

Applicant's arguments filed 3/11/09 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection at pages 5-17 of the response.

Applicant notes that the first aspect of the enablement rejection, having to do with the function of PRF1 in the PI3K cascade, the complexity of the cascade, and the unpredictability arising therefrom did not appear to have been applied against claims 65 and 68 in the previous Action. To clarify, all aspects of the rejection were intended to be applied to claims 65 and 68. The unpredictability that arises from the complexity of the PI3K cascade, its different function in different contexts, and the lack of clarity of the regarding function of PRF1 and its effects on tumor growth, as evidenced by Shoshani (2002) and DeYoung (2008), affects these claims directly.

Regarding the first aspect of the rejection, Applicant asserts that those of skill in the art would have been aware of the complexity of the PI3K network and that PI3K could stimulate apoptosis via IKK or BAD, but that the skilled artisan would have been

able to assess and counteract any possible role of PI3K-mediated inhibition of apoptosis by these pathways. Applicant also notes that the specification provides evidence that inhibition of PRF1 was able to reduce tumor volume in vivo and metastatic activity in vitro, referring to examples 9 and 10 and Figures 6C-D and 11A-B, and asserts that these results would appear to indicate that other pathways by which PI3K can possibly inhibit apoptosis (such as IKK stimulation or BAD inhibition) do not appear to affect the ability of PRF1 to mediate this effect. Applicant further argues that the specification provides evidence that upregulation of HIF1 alpha and Akt upregulation under stress triggers a survival response that counteracts an apoptosis reaction in a cell, and that this can be addressed by down regulating PRF1. This is unpersuasive. The evidence on which Applicant relies appears to have been obtained using a single prostate tumor cell line, PC-3. As discussed above, a large amount of the unpredictability associated with the invention comes form the fact that the elements of the PI3K network that are active in a given cell depend on the type of cell in question as well as the state of the cell at any given time. For example, DeYoung (see above) showed that PRF1 acted as a tumor suppressor in transformed mouse embryo fibroblasts with hyperactivated AKT. PRF1 (REDD1) null cells expressing hyperactivated AKT formed dramatically larger and faster growing tumors than did similar cells expressing wild type PRF1. DeYoung concluded that "[l]oss of REDD1-dependent signaling therefore promotes in vivo tumorigenesis in murine cells." DeYoung also stated that REDD1 was downregulated in 8 of 27 breast carcinoma specimens compared to tissue matched controls, and that a similar frequency of REDD1 downregulation was observed in prostate carcinomas. See

page 246, section entitled "Endogenous REDD1 functions to suppress tumorigenesis in vivo". This is objective post-filing evidence of the unpredictable nature of the function of PRF1 in cancer that substantiates the unpredictability noted by Shoshani in the prior art.

Applicant argues essentially, that this unpredictability could be overcome by experimentation that is not undue, e.g. by assessing the ability of PRF1 to inhibit tumor growth in any number of cell lines that are available to those of skill in the art, or made from actual tumor cells extracted from patients in order to assess the sensitivity of the cells to PRF inhibition. This argument, with respect to cell lines, is unpersuasive because it would be completely unknown if the cell lines would react to PRF inhibition in the same way as the tumor cells in vivo, for the reasons set forth above. The cell lines are not the same as the tumor cells, and there would be no basis for extrapolation in view of the unpredictability established above. Applicant's assertion that it would require at most tedious but not undue experimentation to assay the sensitivity of tumor cells extracted from patients is not supported by evidence. In view of the complexity of the PI3K network, the lack of knowledge regarding how PRF1 interacts with that network and other signaling cascades, and the need to develop culture conditions for each tumor biopsy, it would have been completely unpredictable as to whether or not empirically determined conditions for establishing tumor cells as a primary culture in vitro would alter the cell in ways that would affect its response to PRF1 inhibition. Accordingly it is unclear if such ex vivo tests would provide relevant information as to in vivo activity. Furthermore the claims read on methods of inhibiting migrating cells, but

the specification as filed fails to teach how to locate such cells while they are migrating. One cannot culture cells that one cannot find.

The remainder of Applicant's remarks concern the issue of systemic delivery of siRNA s in vivo. Applicant considers and comments on references relied upon by the Office to establish unpredictability in the art. Applicant's arguments can be distilled to the position that, prior to the time of filing, delivery of oligonucleotides to target cells by systemic administration had been achieved in numerous instances, and that those of skill in the art believed that the results merited the development of clinical trials for oligonucleotide drugs. Thus at the time the invention was filed, one of skill would have believed that oligonucleotide drugs could have been delivered to target cells in vivo by systemic administration, without undue experimentation.

Regarding Opalinska, Applicant asserts that it is clear that the reference supports the opinion that delivery technologies available at the time the application was filed could have been used to successfully deliver nucleic acids such as siRNAs to their cellular targets. This assertion is based on a passage that states that "it is likely that present methods, and/or other evolving technologies, will be used to successfully deliver optimized nucleic acids to their cellular targets." This passage makes no mention of systemic delivery, so it is unclear that the authors believed that current methods, on their own, as used at the time of filing would have allowed enabled systemic delivery.

Regarding Caplen, Applicant also asserts the reference indicates that: siRNA molecules can be successfully delivered to target organs such as liver, spleen,

pancreas, lung, and kidney by high pressure tail vein injection in mice; that siRNA were successfully delivered in vivo via adenoviral vectors and or AAV vectors; and that ES cells and hematopoietic stem cells had been successfully used to mediate RNAi in vivo. These assertions are not persuasive of enablement because the instant claims are drawn to delivery of siRNA molecules, not to delivery of viral vectors or transfected cells, and high pressure tail vein injection is not suitable for use in humans, as previously established.

Regarding Coburn, Applicant notes that the reference indicates that the use of siRNA expression vectors was a great step forward in siRNA delivery. However, this is unpersuasive of enablement because the instant claims are not drawn to delivery of expression vectors, but to contacting cells with siRNA molecules. In any event, the passage relied upon does not make any clear indication regarding systemic, as opposed to local, delivery.

Regarding the Check reference, Applicant notes that while delivery may have been recognized as problematic, clinical efficacy is not required to enable the claims, thus Applicant submits that the invention is enabled as claimed. Applicant further argues that tools existed at the time of the invention that would have allowed one of ordinary skill to obtain successful systemic delivery, relying for support on WO 00/44895, WO 01/75164, Devroe et al (2002), and Ogris (2002). The Office agrees that those of skill in the art had achieved some success in systemic delivery of oligonucleotides at the time of the instant invention. However, the Office has carried out a Wands analysis and established that systemic siRNA delivery was viewed by those of

skill in the art as highly unpredictable at the time of the invention and afterwards, the specification provides no working example, and no systemic delivery guidance that was not available in the prior art. In view of this analysis, combined with the previously discussed unpredictability with regard to the function of PRF1 in cancer, one of skill in the art could not use the invention without undue experimentation.

At pages 14-18 of the response, Applicant argues that the Opalinska reference referred to a variety of clinical trials and that many of these provided some evidence of disease remission or treatment. Applicant relies for support on Waters et al (2000), Jansen (et al 2000), Yacshyn et al (2000), Numenaitis et al (1999), Cunningham (2001), Cunningham (2000), and Yuen et al (1999).

As Applicant notes, each of these was a phase I trial, and so was not geared toward obtaining a clinical response. In each case the sample sizes were small. In each of the references in which a number of possible positive responses was detected, a greater number of patients did not show a possible positive response. Accordingly, the results for each of these studies indicated that it was more likely than not that the oligonucleotide would have no effect at the dose tested. Also, due to the small sample sizes, it is not clear that any positive result was due to the antisense drug, as opposed to chance. It is also noted that none of them deals with siRNA, or the delivery of RNA oligonucleotides. Accordingly these references do not provide persuasive evidence of that systemic oligonucleotide delivery is generally enabled. Furthermore, the references do not address the function of PPRF1 in cancer.

For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official

central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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